

European Heart Journal: Acute Cardiovascular Care

<http://acc.sagepub.com/>

Prognostic impact of admission blood glucose for all-cause mortality in patients with acute coronary syndromes: added value on top of GRACE risk score

Ana T Timóteo, Ana L Papoila, Pedro Rio, Fernando Miranda, Maria L Ferreira and Rui C Ferreira

European Heart Journal: Acute Cardiovascular Care published online 31 March 2014

DOI: 10.1177/2048872614528858

The online version of this article can be found at:

<http://acc.sagepub.com/content/early/2014/03/31/2048872614528858>

Published by:

European Society of Cardiology



EUROPEAN
SOCIETY OF
CARDIOLOGY®

ESC Working Group on Acute Cardiac Care



Acute
Cardiovascular
Care Association
A Registered Branch of the ESC

and

<http://www.sagepublications.com>

Additional services and information for *European Heart Journal: Acute Cardiovascular Care* can be found at:

Email Alerts: <http://acc.sagepub.com/cgi/alerts>

Subscriptions: <http://acc.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [OnlineFirst Version of Record](#) - Mar 31, 2014

[What is This?](#)

Prognostic impact of admission blood glucose for all-cause mortality in patients with acute coronary syndromes: added value on top of GRACE risk score

European Heart Journal: Acute Cardiovascular Care
1–7

© The European Society of Cardiology 2014

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/2048872614528858

acc.sagepub.com



Ana T Timóteo¹, Ana L Papoila^{2,3}, Pedro Rio¹, Fernando Miranda⁴, Maria L Ferreira¹ and Rui C Ferreira¹

Abstract

Background: Abnormal glucose metabolism is a predictor of worse outcome after acute coronary syndrome (ACS). However, this parameter is not included in risk prediction scores, including GRACE risk score. We sought to evaluate whether the inclusion of blood glucose at admission in a model with GRACE risk score improves risk stratification.

Methods: Study of consecutive patients included in a single centre registry of ACS. Our primary endpoint was the occurrence of all-cause mortality at one-year follow-up. The ability of the two logistic regression models (GRACE risk score alone and in combination with blood glucose) to predict death was analysed. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI), with corresponding 95% confidence intervals (CIs), were also calculated.

Results: We included 2099 patients, with a mean age of 64 (SD=13) years, 69% males. In our sample, 55.1% presented with ST-segment elevation ACS and 13.1% in Killip class ≥ 2 . Only 25% were known diabetic at admission. In-hospital mortality was 5.8% and 9.7% at one-year follow-up. The best cut-point for blood glucose was 160 mg/dl (sensitivity 62% and specificity 68%), and 35.2% of the patients had increased levels. This group was elderly, had more prevalence of cardiovascular risk factors, worse renal function and GRACE score as well as more frequently Killip class ≥ 2 . Treatment was similar in both groups besides less frequent use of clopidogrel in high glycaemic patients. The hyperglycaemia group had higher one-year mortality (17.2% vs. 5.6%, $p<0.001$). Moreover, binary blood glucose remained a predictor of death independently of the GRACE risk score and the presence of diabetes (odds ratio (OR) 1.99, 95% CI 1.40–2.84, $p<0.001$). The inclusion of blood glucose, as a continuous variable, in a logistic regression model with GRACE score, increased the area under the ROC curve from 0.80 to 0.82 ($p=0.018$) as well as the goodness-of-fit and was associated with an improvement in both the NRI (37%) and the IDI (0.021), suggesting effective reclassification.

Conclusions: A blood glucose level on admission ≥ 160 mg/dl is an independent predictor of mortality in medium-term follow-up. It offers an incremental predictive value when added to the GRACE risk score, although with a modest magnitude of improvement, probably due to the high predictive performance of the GRACE risk score alone.

Keywords

Admission blood glucose, GRACE risk score, acute coronary syndromes, prognosis

Received: 18 November 2013; accepted: 3 March 2014

¹Cardiology Department, Santa Marta Hospital, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

²Biostatistics Department, CEAUL, Medical Sciences Faculty, New University of Lisbon, Portugal

³Research Department, Hospital Dona Estefânia, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

⁴Clinical Pathology Department, Santa Marta Hospital, Centro Hospitalar de Lisboa Central, Lisbon, Portugal

Corresponding author:

Ana Teresa Timóteo, Cardiology Department, Hospital Santa Marta, Rua Santa Marta, 1169-024 Lisboa, Portugal.

E-mail: ana_timoteo@yahoo.com

Introduction

Elevated admission blood glucose is an important marker of worse outcome in patients with myocardial infarction.¹ It is useful in patients both with and without diabetes.^{2–9} It is usually caused by stress hyperglycaemia induced by catecholamines, which, in turn, are correlated with myocardial lesion extension.¹ However, risk scores applied in clinical practice do not include this variable.

The Global Registry of Acute Coronary Events (GRACE) risk score is a validated and established score for risk stratification of patients with acute coronary syndromes, obtained from a multicentre registry.¹⁰ It is used worldwide with very good predictive value for short- and medium-term all-cause mortality. It incorporates several clinical and laboratorial variables to which a score is given to obtain the final score. Although better than previous risk scores, some patients are still incorrectly classified and some improvement in predictive accuracy would be important, particularly with the use of an easily obtainable variable.

Few studies are found in the literature that assessed the incremental prognostic value of admission blood glucose in combination with the GRACE risk score. However, these studies are somewhat small and showed no significant benefit.^{11,12} We sought to investigate the incremental value of admission blood glucose when considered with the GRACE risk score for the prediction of all-cause mortality at one-year, in a large sample of patients with the whole spectrum of acute coronary syndromes.

Methods

This is an observational study of all consecutive patients admitted to our intensive care unit (ICU) with ACS (with and without ST-segment elevation) during the years 2008 to 2010. Data were collected prospectively and recorded on a computer database of ACS patients admitted to our institution's ICU (single-centre registry of ACS). Inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 hours of admission. This could be associated with new or presumed new significant ST-segment–T wave changes/new left bundle branch block or elevated levels of biomarkers of myocardial damage (cardiac troponin I and creatine kinase). Myocardial infarction was defined by a rise and/or fall of cardiac troponin I with at least one value above 0.06 ng/ml. We evaluated demographic characteristics of the patients, risk factors for coronary artery disease, previous cardiac history, laboratorial data and vital signs on admission as well as in-hospital treatment. Automated laboratory equipment (Beckman Coulter LXi™ analyser) was used for glucose determination by the glucose-oxidase method (coefficient of variation: 2.0%).

We enrolled all consecutive patients if they had a record of admission blood glucose. There were no exclusion criteria.

Patients with increased blood glucose on admission were defined by a cut-off obtained with the statistical analysis described below.

Hypertension, diabetes and hyperlipidaemia were defined as either previously known or on specific therapy. Patients that had smoked during the previous six months were classified as smokers and were self-reported. Estimated glomerular filtration rate (eGFR) was calculated according to the Cockcroft–Gault formula.¹³ For each patient, a numerical scoring according to the previously described GRACE risk score was calculated from the initial clinical history, electrocardiogram and laboratory values collected on admission.¹⁰

Follow-up was obtained for every patient that survived to discharge by reviewing the medical records and/or by telephone interview with the patient or family members at 30 days and one year after admission. Follow-up information was obtained in 99.8% of the patients. The study primary endpoint was all-cause mortality at one-year follow-up.

The study complies with the Declaration of Helsinki and informed consent was obtained from all the subjects.

Statistical analysis

Continuous variables are expressed as mean (SD) and groups were compared with Student's *t*-test. Categorical variables are expressed as percentage and Pearson's chi-squared test or Fisher's exact test were used, whenever appropriate.

Two logistic regression models were fitted to the data, one with the GRACE risk score alone and the other with the inclusion of blood glucose as a continuous variable. Predictive and discriminative abilities of these models were assessed by the Hosmer–Lemeshow goodness of fit test and by the area under the receiver operating characteristic (ROC) curve (AUC), respectively. The former compares the observed frequencies of patients with the event of interest with the expected frequencies based on the values of the estimated probabilities obtained by the logistic regression models. In this test, a high *p*-value (non-significant) indicates that the model is performing well and has a good fit. The AUC ranges from 0 to 1 and provides a measure of the model's ability to discriminate between those subjects who experience the outcome of interest and those who do not. An AUC equal to 0.5 means no classification accuracy. To compare the AUCs from each of these models, the method described by DeLong et al. was used.¹⁴

Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also calculated. The net proportion of patients who died (with events) with higher probabilities of death (NRI_{events}) and of patients who did not die (without events) with lower probabilities of death ($NRI_{non-events}$), were calculated considering both models. The NRI is the sum of NRI_{events} and $NRI_{non-events}$ and quantifies the correctness of upward and

downward reclassification or movement of predicted probabilities as a result of adding a new marker.¹⁵ The IDI is a measure of the improvement in prediction and may be viewed as the difference between improvement in average sensitivity and average 1-specificity.¹⁶

Regarding the categorization of blood glucose, minimum *p*-value approach was used. This method obtains the best cut-point from a grid of marker values that is associated with the minimum chi-squared *p*-value.¹⁷ A new logistic regression model was fitted considering the GRACE risk score and the categorized blood glucose, as independent variables.

For all comparisons, a *p*-value ≤ 0.05 was considered statistically significant. Whenever appropriate, 95% confidence intervals (CIs) were calculated.

Statistical analysis was carried out using IBM SPSS Statistics, Version 19.0 (IBM Corp., North Castle, NY, USA) and R software.¹⁸

Results

From a total of 2216 consecutive patients included in our registry, 2099 had information about admission blood glucose and were included in the study, with a mean age of 64 (SD=13) years, 69% males. The population baseline characteristics are described in Table 1. The in-hospital, 30-day and one-year mortality rates were 5.1%, 5.8% and 7.8% respectively.

By ROC curve analysis, the AUC of blood glucose for the prediction of one-year mortality was 0.68 (95% CI 0.64–0.72). Univariable analysis showed that blood glucose at admission, as a continuous variable, is a predictor of outcome (OR 1.07, 95% CI 1.05–1.08, *p* < 0.001, per 10 mg/dl increase) and it remained an independent predictor of mortality after adjustment for the GRACE risk score and for the presence of diabetes (OR 1.04, 95% CI 1.02–1.06, *p* < 0.001).

Models with GRACE risk score alone and after inclusion of blood glucose were then fitted to the data. The AUC increased significantly after the inclusion of blood glucose in the model (AUC=0.80 vs. AUC=0.82; *p*=0.018) (Figure 1) as did the goodness of fit (Table 2). Overall, the inclusion of blood glucose in a model with GRACE risk score was associated with a NRI of 37%, suggesting effective reclassification. Significant reclassification occurred mainly in the non-events group. In fact, for NRI non-events, a net 48% of patients who did not die had a substantial and significant reduction of the calculated risk. The IDI again showed that the model performance was improved by adding blood glucose to the GRACE risk score (IDI = 0.021) and, although modest, it was statistically significant.

Aware of the importance of biomarker cut-points in daily clinical practice, minimum *p*-value approach was used in order to find the blood glucose level that best

discriminates the occurrence of all-cause mortality at one-year follow-up. A value of 160 mg/dl was obtained (Figure 2), with a sensitivity of 62% and a specificity of 68%. Patients with increased blood glucose were older, less often males, and had more risk factors for coronary artery disease, as well as previous stroke/transient ischemic attack (Table 1). They presented more often as a STEMI and with signs of heart failure. Renal insufficiency was more prevalent. They were more often submitted to coronary angiography and had more multivessel disease. Treatment was similar, except for clopidogrel, which was less frequently prescribed in patients with increased admission glucose. Mortality was significantly higher in this group (*p*<0.001).

Finally, the results of a new logistic regression model showed that blood glucose, as a binary variable, remained a predictor of death independently of the GRACE risk score and the presence of diabetes (OR 1.99, 95% CI 1.40–2.84, *p*<0.001).

Discussion

Elevated blood glucose level at admission for myocardial infarction is associated with worse outcome in both non-diabetic and diabetic patients.^{1–9} In fact, in a broad ACS population, hyperglycaemia at admission is a short-term and long-term prognostic marker.¹ A high glucose level at admission is often attributed to ‘stress hyperglycaemia’ and might reflect an acute response to the hyperadrenergic state, with catecholamine release and induction of glycogenolysis.¹ It is also associated with the increase in free fatty acids, insulin resistance, inactivation of nitric oxide and the production of oxygen reactive species, generating oxidative stress, as well as enhanced thrombin formation, platelet activation and fibrin clot resistance to lysis.^{1,19} Hyperglycaemia is associated with impaired coronary flow before reperfusion therapy in ST-elevation myocardial infarction patients.²⁰

A report from the GRACE registry showed that short-term and six-month mortality was increased significantly with higher admission glucose levels in patients across the whole spectrum of acute coronary syndromes.¹ This association is probably mainly driven by an increased risk of early death, consistent with the paradigm that admission glucose level is a marker of stress rather than a reflection of a general glucometabolic state.²¹ A U-shaped curve of risk associated with admission glucose level is described, consistent with previous reports of adverse outcome associated with low levels (< 100 mg/dl) in patients presenting with an acute myocardial infarction and in diabetic patients with ACS.^{1,22} It might be related to inadequate stress response. This registry also showed the association between fasting glucose levels and short-term and six-month mortality, suggesting that this might be a better independent marker than admission glucose level.¹

Table 1. Clinical characteristics of both groups according to glucose levels.

	Total n=2099	Glucose < 160 mg/dl n=1361	Glucose ≥ 160 mg/dl n=738	p-value
Age (years)	64 ± 13	63 ± 13	66 ± 14	<0.001
Male gender (%)	69.1	71.1	65.3	0.007
Risk factors (%)				
Hypertension	65.7	63.0	70.7	<0.001
Hyperlipidaemia	49.8	51.5	46.6	0.036
Diabetes	25.5	10.9	52.4	<0.001
Smoking	36.4	40.4	29.0	<0.001
Previous history (%)				
Myocardial infarction	15.7	15.5	16.1	0.756
PCI	10.5	11.5	8.7	0.055
CABG	4.2	3.7	5.1	0.159
Stroke/TIA	6.3	5.1	8.5	0.002
Initial presentation				
STEMI (%)	55.1	52.5	59.8	0.002
Killip class > I (%)	13.1	8.4	21.8	<0.001
Heart rate (beats/min)	78 ± 19	76 ± 18	81 ± 21	<0.001
Systolic blood pressure (mmHg)	133 ± 28	134 ± 28	132 ± 29	0.121
Laboratory data				
eGFR < 60 ml/min per 1.73 m ² (%)	28.1	24.2	35.4	<0.001
Blood glucose (mg/dl)	163 ± 82	119 ± 21	244 ± 90	<0.001
GRACE risk score	145 ± 36	138 ± 34	158 ± 36	<0.001
LVEF < 35% (%)	7.5	5.2	11.8	<0.001
Coronary angiography (%)	76.9	75.5	79.5	0.032
Multivessel disease	66.8	63.1	72.7	<0.001
Treatment (%)				
ASA	97.4	97.7	96.7	0.234
Clopidogrel	93.3	94.1	91.7	0.046
ACEI	86.7	86.3	87.3	0.596
Beta-blocker	81.8	82.4	80.9	0.438
Statin	92.6	93.3	91.2	0.093
PCI	74.6	74.2	75.3	0.607
CABG	1.1	1.0	1.4	0.535
All-cause mortality (%)				
In-hospital mortality	5.1	2.8	11.2	<0.001
One-year mortality	7.8	5.6	17.2	<0.001

PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; TIA: transient ischemic attack; STEMI: ST elevation myocardial infarction; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; ASA: acetylsalicylic acid; ACEI: angiotensin converting enzyme inhibitor

Two previously published papers showed no benefit in risk stratification after ACS with the inclusion of admission blood glucose in a logistic regression model with GRACE risk score. However, the samples were relatively small and in one case only hospital mortality was analysed.^{11,12}

Correia et al. studied a small sample (148 patients) with only non-ST segment elevation ACS.¹¹ There was no benefit in either AUC or NRI. Admission blood glucose was introduced directly inside the GRACE risk score model without any type of validation. De Mulder et al. studied a larger sample (550 patients), but the inclusion period was from 2003 to 2006, and does not reflect contemporary treatment.¹² Both

AUC and NRI improvement showed a trend, although not of statistical significance. The data from our large and unselected population confirmed that admission glucose is an independent predictor of all-cause mortality in the whole spectrum of acute coronary syndromes, even after adjustment for diabetic status and GRACE risk score. They also showed significant benefit in risk stratification after the inclusion in a model with the GRACE risk score.

Mere associations with incident all-cause mortality, although important, do not automatically mean that adding a new marker to traditional risk prediction models will improve outcome risk prediction. Therefore, we performed

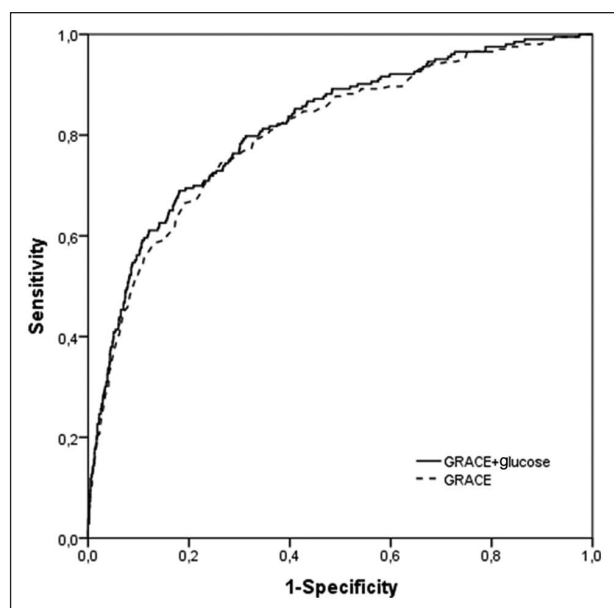


Figure 1. ROC curve analysis comparing the GRACE risk score and the new model with the inclusion of blood glucose (p -value = 0.018).

Table 2. Statistics for model improvement with the addition of blood glucose.

Events (n)	203
Non-events (n)	1896
Continuous NRI (%)	
cNRI _{events}	-10 (-24 to 3)
cNRI _{non-events}	48 (44 to 52)
cNRI	37 (23 to 52)
IDI statistics	
IDI _{events}	0.019
IDI _{non-events}	0.002
IDI	0.021 (0.008 to 0.033)
AUC	
GRACE risk score	0.80 (0.77–0.84)
Combination model	0.82 (0.79–0.85)
Difference (p -value)	0.018
Goodness of fit (GRACE risk score) ^a	0.732
Goodness of fit (combination model) ^a	0.946

The 95% confidence intervals are shown in parenthesis.

^aHosmer–Lemeshow goodness of fit test (p -value).

NRI: net reclassification improvement; IDI: integrated discrimination improvement; AUC: area under the receiver operator characteristic curve

tests to discriminate and calibrate different prediction models. Discriminative analysis of a model with GRACE risk score alone and after admission glucose inclusion showed that the AUC increased significantly. The predictive performance also improved. Considering the other new statistical metrics, recently proposed, to quantify the degree of correct reclassification, the inclusion of glucose

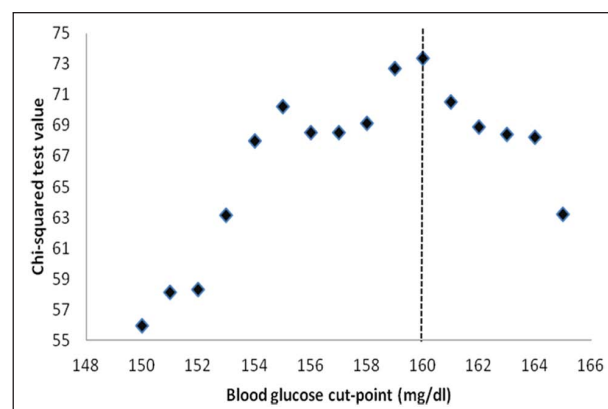


Figure 2. Resulting plot of minimum p -value approach. Chi-squared values measuring the association between death at one-year follow-up and dichotomized blood glucose are plotted as a function of different blood glucose cut-points. The shape of the plot suggests the existence of a cut-point at 160 mg/dl.

in a model with GRACE risk score was associated with a NRI of 37%, suggesting effective reclassification. The new model better identifies the group without events. The IDI again showed that the model performance was significantly, although slightly, improved by adding glycaemia to the GRACE risk score.

The magnitude of improvement was small. However, in the presence of a fairly robust risk score, such as in the case of the GRACE risk score, the quantitative improvement in model performance introduced by adding new variables to the existing model is expected to be small. Also the new model better identifies those who do not have events than those who do. The new model significantly reduced the calculated risk in 48% of those without events. Thus the new model (with the addition of admission blood glucose to GRACE score) is better at identifying ‘truly low-risk’ patients and is as good as in identifying patients who develop events. This might not be ideal when we are evaluating a risk score to identify high-risk patients. However, recent cardiovascular disease guidelines are encouraging a practice shift toward greater focus on identification of ‘truly low-risk’ patients instead of focusing on identification of high-risk patients. This allows a better selection of patients avoiding unnecessary interventions that might increase costs as well as the risk of procedure-related adverse events.

Limitations

This is a single-centre study, which might limit its conclusions. It is also a retrospective study. It might not be applicable to other populations with different baseline characteristics. In particular, our population has a predominance of ST elevation myocardial infarction patients, explained by the fact that we are a tertiary centre which receives many patients from other hospitals for primary percutaneous coronary intervention. However, this does not reflect the

distribution in other cohort studies of ACS and some caution should be used when translating our results for other cohorts.

The cut-off proposed by the present work was not externally validated. However, other authors from Spain and Italy (Mediterranean countries) proposed similar cut-offs (140 mg/dl and 170 mg/dl, respectively).^{23–25} Other, Eastern European, countries suggest higher cut-points (≥ 200 mg/dl).^{26,27} Probably there is some genetic/environmental explanation for these results and local studies seem to be important.

Conclusions

In a population of patients with the whole spectrum of acute coronary syndromes, blood glucose adds prognostic information to established risk factors, even in combination with the GRACE risk score. A level at admission ≥ 160 mg/dl is an independent predictor of mortality in medium-term follow-up. We encourage its wider use.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The statistical analysis performed by ALP was supported by the Fundação Nacional para a Ciência e Tecnologia, Portugal – FCT, under the project PEst-OE/MAT/UI0006/2014.

References

1. Sinnaeve PR, Steg PG, Fox KAA, et al. Association of elevated fasting glucose with increased short-term and 6-month mortality in ST-segment elevation and non-ST-segment elevation acute coronary syndromes. *Arch Intern Med* 2009; 169: 402–409.
2. Timmer JR, van der Horst IC, Ottervanger JP, et al., on behalf of Zwolle Myocardial Infarction Study Group. Prognostic value of admission glucose in non-diabetic patients with myocardial infarction. *Am Heart J* 2004; 148: 399–404.
3. Otten R, Kline-Rogers E, Meier DJ, et al. Impact of prediabetic state on clinical outcomes in patients with acute coronary syndrome. *Heart* 2005; 91: 1466–1468.
4. Rocha S, Nabais S, Magalhães S, et al. Admission glycemia: A predictor of death after acute coronary syndrome in non-diabetic patients? *Rev Port Cardiol* 2007; 26: 1367–1377.
5. Svensson AM, McGuire DK, Abrahamsson P, et al. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005; 26: 1255–1261.
6. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet* 2000; 355: 773–778.
7. Monteiro S, Monteiro P, Gonçalves F, et al. Hyperglycemia at admission in acute coronary syndrome patients: Prognostic value in diabetics and non-diabetics. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 155–159.
8. Norhammar A, Tenerez A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: A prospective study. *Lancet* 2002; 359: 2140–2144.
9. Stranders I, Diamant M, van Gelder RE, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med* 2004; 164: 982–988.
10. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study (GRACE). *BMJ* 2006; 333: 1091–1094.
11. Correia LC, Rocha MS, Bittencourt AP, et al. Does acute hyperglycemia add prognostic value to the GRACE score in individuals with non-ST elevation acute coronary syndromes? *Clin Chim Acta* 2009; 410: 74–78.
12. de Mulder M, van der Ploeg T, de Waard GA, et al. Admission glucose does not improve GRACE score at 6 months and 5 years after myocardial infarction. *Cardiology* 2011; 120: 227–234.
13. Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
14. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988; 44: 837–845.
15. Pencina MJ, D'Agostino RB and Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011; 30: 11–21.
16. Huang Y, Pepe MS and Feng Z. Evaluating the predictiveness of a continuous marker. *Biometrics* 2007; 63: 1181–1188.
17. Mazumdar M and Glassman JR. Tutorial in biostatistics – categorizing a prognostic variable: Review of methods, code for easy implementation and applications to decision-making about cancer treatments. *Stat Med* 2000; 19: 113–132.
18. R Core Team (2013). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>.
19. Undas A, Wiek I, Stepień E, et al. Hyperglycemia is associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis in patients with acute coronary syndromes. *Diabetes Care* 2008; 31: 1590–1595.
20. Timmer JR, Ottervanger JP, de Boer MJ, et al. Zwolle Myocardial Infarction Study Group. Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2005; 45: 999–1002.
21. Zeller M, Cottin Y, Brindisi MC, et al. Impaired fasting glucose and cardiogenic shock in patients with acute myocardial infarction. *Eur Heart J* 2004; 25: 308–312.
22. Pinto DS, Skolnick AH, Kirtane AJ, et al. TIMI Study Group. U-shaped relationship of blood glucose with adverse outcomes among patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2005; 46: 178–180.
23. Sanjuán R, Nunez J, Blasco ML, et al. Prognostic implications of stress hyperglycemia in acute ST elevation myocardial infarction. Prospective observational study. *Rev Esp Cardiol* 2011; 64: 201–207.

24. Lazzeri C, Valente S, Chiostrì M, et al. In-hospital peak glycaemia and prognosis in STEMI patients without earlier known diabetes. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 419–423.
25. Corrada E, Cappelleri A, Belli G, et al. Admission glycaemia and markers of inflammation are independent outcome predictors in primary PCI in non-diabetic patients. *Minerva Cardioangiol* 2008; 56: 445–452.
26. Kazberuk AT, Kozuch M, Malyszko J, et al. What level of hyperglycaemia on admission indicates a poor prognosis in patients with myocardial infarction treated invasively? *Kardiol Pol* 2012; 70: 564–572.
27. Bronisz A, Kozinski M, Magielski P, et al. Stress hyperglycaemia in patients with first myocardial infarction. *Int J Clin Pract* 2012; 66: 592–601.